Evaluation of Safety and Clinical Outcomes of Sotrovimab in Patients Infected with SARS-CoV-2 in Real-World Clinical Practice

Interim Report of General Drug Use Investigation

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ABSTRACT

Objectives: To evaluate data on the safety and clinical outcomes of sotrovimab in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in real-world clinical practice.

Methods: Included patients were infected with SARS-CoV-2, had risk factors for progression to severe SARS-CoV-2 infection, did not require oxygen therapy due to SARS-CoV-2 infection at baseline and received sotrovimab for the first time (target sample size: 630 patients for enrollment). The observation period was 29 days, counting the date of sotrovimab treatment as day 1. Inpatients were observed until discharge from hospital or transfer to another hospital. Outpatients were observed on day 1 only. Safety was evaluated through occurrence of adverse drug reactions (ADRs), and ADRs related to "serious hypersensitivity such as anaphylaxis, infusion reactions" were evaluated as events of special interest. Progressor rate was evaluated as the endpoint of clinical outcomes.

Results: Between 31 January and 19 August 2022, 512 patients were enrolled in this study, and 346 case report forms (CRFs) were finalized. Among 346 patients in the safety analysis population, 9 patients (2.6%) experienced ADRs. The reported ADRs were "pyrexia" in 7 patients (2.0%), and "COVID-19 pneumonia","dyspnoea","oropharyngeal pain", and "eczema" in 1 patient (0.3%). Two ADRs of special interest ("dyspnoea" and "eczema") were reported. The percentage of progressors in the 246 patients included in

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the clinical outcome analysis population was 0.4% (1/246 patients). Regarding the progressor rate by SARS-CoV-2 sampling period, 0.8% (1/118 patients) progressed to severe SARS-CoV-2 infection from 31 January to 27 March 2022 (BA.1 dominant period) and there were no progressors to severe SARS-CoV-2 infection (0.0%, 0/128 patients) from 28 March to 19 June 2022 (BA.2 dominant period).

Conclusions: This interim report did not identify any new concerns regarding the safety and clinical outcomes of sotrovimab. The study is ongoing and will provide additional data on the real-world safety and effectiveness of sotrovimab.

INTRODUCTION

SARS-CoV-2 (novel coronavirus) is a type of β coronavirus[1], and SARS-CoV-2 infection (coronavirus disease 2019 or COVID-19) is continuing to spread around the world since it was first reported in Wuhan, China in December 2019[2]. According to the World Health Organization (WHO), as of August 2022, the cumulative number of people infected with SARS-CoV-2 worldwide had reached approximately 590 million, and approximately 6.4 million deaths had been reported[3]. In Japan, as of August 2022, the cumulative number of infected people was approximately 17 million, and the number of deaths had reached approximately 37,000[4].

Symptoms of SARS-CoV-2 infection include pyrexia, cough, shortness of breath, headache, malaise, pharyngodynia, sputum, runny nose, inappetence, haemoptysis, myalgia, and diarrhoea. The majority of patients infected with SARS-CoV-2 recover without progression to severe infection, however, approximately 14% of patients require hospitalization and oxygen therapy after progression to severe infection, and approximately 5% require treatment in the intensive care unit (ICU)[5]. In addition, data on risk factors for SARS-CoV-2 infection are being accumulated ; common risk factors in Japan include age 65 years or older, malignant tumour, chronic respiratory disease, chronic kidney disease, diabetes mellitus, hypertension, dyslipidaemia, cardiovascular disease, cerebrovascular disease, obesity, smoking, immunodeficiency secondary to solid organ transplantation, the second half of pregnancy, use of immunosuppressant medications or modulators, and human immunodeficiency virus infection[6].

In Japan, as of 19 August 2022, remdesivir, molnupiravir, nilmatrelvir/ritonavir, sotrovimab, and casirivimab/imdevimab can be used for patients with mild to moderate I (no respiratory failure) SARS-CoV-2 infection, and remdesivir, steroids (dexamethasone, etc.), baricitinib and tocilizumab are available for patients with moderate I (with respiratory failure) to severe SARS-CoV-2 infection[6].

Sotrovimab is a human monoclonal antibody (mAb) that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2. It has a dual mechanism of action, with the ability to neutralize the virus as well as recruit the immune system to kill already infected cells *in vitro* and *in vivo*. It has been reported that the epitope of sotrovimab is present in a different part of the spike protein of SARS-CoV-2 from the angiotensin-converting enzyme 2 (ACE2) receptor binding site and is conserved[7]. Sotrovimab was approved for treatment of SARS-CoV-2 infection in the United States (May 2021 to April 2022, emergency use authorization [EUA]), Australia (August 2021, provisional approval), the United Kingdom (December 2021, Conditional Marketing Autho-

rization) and Europe (December 2021), based on the results of the phase Ⅱ/Ⅲ COMET-ICE (COVID-19 Monoclonal Antibody Efficacy Trial-Intent to Care Early) clinical trial[8,9]. COMET-ICE was conducted overseas in non-hospitalized patients with mild to moderate SARS-CoV-2 infection who have a high risk of disease progression. In the final analysis of the primary endpoint, 29-day hospitalization or mortality events occurred in 1% (6/528) of the sotrovimab cohort and 6% (30/529) of the placebo cohort, a 79% relative risk reduction[9]. In Japan, special approval for emergency (SAE) use of sotrovimab was obtained in September 2021 for the indication of "infection caused by SARS-CoV-2". However, based on *in vitro* studies showing a shift in the neutralization activity of sotrovimab against omicron BA.2 relative to wild-type strain, the U.S. Food and Drug Administration (FDA) deauthorized sotrovimab in the United States as of 5 April 2022[10]. In Japan, although sotrovimab remains authorized, the following warning statement was added to the Japanese Package Insert of sotrovimab in April 2022 ; "For omicron (B.1.1.529/BA.2), sotrovimab should be considered for administration when other medications cannot be administered, because effectiveness of sotrovimab may be decreased"[11]. The clinical impact of this *in vitro* neutralization is unknown, and sotrovimab remains authorized in Australia, Europe and United Kingdom as well as Japan.

Sotrovimab was shown to be well tolerated in a Japanese population in a phase Ⅰ clinical study which compared the safety, tolerability and pharmacokinetics of a 500 mg single intravenous infusion (IV) in Japanese and Caucasian healthy adults[12]. However, the safety and clinical outcomes of sotrovimab in a Japanese population in real-world clinical practice have not been evaluated. Of particular interest is the occurrence of adverse drug reactions (ADRs) related to "serious hypersensitivity such as anaphylaxis, infusion reactions", which was identified as an important identified risk in the Japanese Risk Management Plan (J-RMP) of sotrovimab[13], and the effectiveness of sotrovimab against omicron BA.2 in the real-world setting. Here, we report the interim results of a general drug use investigation (observational study) in Japan, which was designed to evaluate the safety and clinical outcomes of sotrovimab treatment in patients infected with SARS-CoV-2 in real-world clinical practice.

PATIENTS AND METHODS

1 Patients and study methods

Included patients were infected with SARS-CoV-2, had risk factors for progression to severe SARS-CoV-2 infection, did not require oxygen therapy due to SARS-CoV-2 infection at baseline and received sotrovimab for the first time. Enrollment in this study was started in January 2022 using a central enrollment method, in which enrollment at each site was optional and not all patients who were treated with sotrovimab at a site might have been enrolled, and investigators enrolled patients within 14 days after the date of sotrovimab administration. Target sites were mainly selected from medical institutions designated for infectious diseases, regional medical care support hospitals and special functioning hospitals in Japan. Patients received a single 500 mg IV dose of sotrovimab. The target sample size in this study was 630 patients. The observation period per patient was between day 1 and 29, counting the date of sotrovimab treatment as day 1. Inpatients were observed until discharge from hospital or transfer to another hospital. Outpatients were observed on day 1 only. In Japan, each prefecture determines whether a patient infected with

SARS-CoV-2 should be hospitalized or not based on the severity of symptoms, the presence or absence of risk factors for progression to severe SARS-CoV-2 infection, and the number of patients infected with SARS-CoV-2 in each region[14]. These latter two points differ from the standard clinical practice in countries where COMET-ICE trial data[9] were generated, where patients are not routinely hospitalized, largely only for immediate clinical need.

2 Study items

1) Patient characteristics

The following characteristics were collected : gender, year of birth, hospitalization status, weight and height, smoking history, presence or absence of comorbidities (renal impairment, hepatic impairment, allergy, other) and name of comorbidities, oxygen therapy for diseases other than SARS-CoV-2 infection, oxygen therapy for SARS-CoV-2 infection, types of risk factors for progression to severe SARS-CoV-2 infection, sampling date of nucleic acid detection tests or antigen tests diagnosing as SARS-CoV-2 positive, test for SARS-CoV-2 infection variants and variant type, severity of SARS-CoV-2 infection, onset date of SARS-CoV-2 infection symptom, and vaccination against SARS-CoV-2 infection.

2) Safety evaluation

For all adverse events (AEs) occurring after sotrovimab treatment, name of AEs, onset date, outcome, seriousness, and relationship with sotrovimab treatment were investigated. We defined a serious AE as any AE that : 1) results in death ; 2) is life-threatening ; 3) requires inpatient hospitalization or prolongation of existing hospitalization ; 4) results in persistent or significant disability/incapacity ; 5) is a congenital anomaly/birth defect ; 6) is any other event or reaction judged to be medically important. AEs that cannot be excluded as being related to sotrovimab were regarded as ADRs. For the events reported by the investigators, the appropriate lowest level terms (LLTs) were selected from the Japanese version of the Medical Dictionary for Regulatory Activities (MedDRA/J : Version 24.1) of the international medical terminology developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) ; the corresponding preferred terms (PTs) were evaluated. Based on J-RMP of sotrovimab[13], this study included "serious hypersensitivity such as anaphylaxis, infusion reactions" in the safety analysis as events of special interest. Among reported ADRs, events corresponding to the following were handled as a concern in the safety specification,"serious hypersensitivity such as anaphylaxis and infusion reactions".

A) Events which exclude both High Level Term (HLT) "Injection Site Reactions" and HLT "Infusion Site Reactions" from "Hypersensitivity" (narrow) in Standardised MedDRA Queries (SMQs)

B) "Anaphylactic reaction" (broad) in SMQs

3) Clinical outcome evaluation

(1) Definition of percentage of progressors

Clinical outcome was evaluated using the proportion of progressors. Among those who could be evaluated during the period from the date of sotrovimab treatment to the end of the observation period (the shorter period between 29 days and hospitalization period), patients were defined as progressors if any of the following applied :

a) Patients who receive oxygen at a rate of >5 liters/min as a concomitant therapy for exacerbation of SARS-CoV-2 infection

b) Patients who receive any of the following as a concomitant therapy for exacerbation of SARS-CoV-2 infection

- Non-invasive positive pressure ventilation

(NPPV)
- Invasive mechanical ventilation (IMV)
- Extracorporeal membrane oxygenation (ECMO)

c) Patients who require admission to high care unit (HCU) or ICU for exacerbation of SARS-CoV-2 infection in study sites with HCU or ICU

d) Patients who are transferred to another hospital for exacerbation of SARS-CoV-2 infection to receive any of a) to c) mentioned above

e) Patients who die from exacerbation of SARS-CoV-2 infection

This endpoint is set expecting to correspond to the primary endpoint of the COMET-ICE trial (proportion of participants who have progression of COVID-19 through day 29 as defined as hospitalization>24 hours for acute management of illness, or death) which was conducted in non-hospitalized patients overseas, as a certain number of patients who had risk factors for progression to severe SARS-CoV-2 infection in Japan were routinely hospitalized at the beginning of treatment based on the criteria of each prefecture, even if their severity was not severe as mentioned above[14].

(2) Percentage of progressors by sampling period

According to the genome surveillance data from the National Institute of Infectious Diseases (NIID)[15] and genome surveillance data based on samples from private testing institutions[16], the most commonly detected SARS-CoV-2 variant lineages (accounting for more than 50% of the total number of tests) during the period "31 January to 27 March 2022" and "28 March to 19 June 2022" were "omicron BA.1" and "omicron BA.2", respectively. Therefore, the percentage of progressors was monitored by dividing the period into two: "31 January to 27 March 2022" (period during which omicron BA.1 was estimated to be dominant in Japan, hereinafter called "BA.1 dominant period") and "28 March to 19 June 2022" (period during which omicron BA.2 was estimated to be dominant in Japan, hereinafter called "BA.2 dominant period"). As the rationale for the "BA.1 dominant period" and the "BA.2 dominant period", the FDA restricted the use of sotrovimab in regions where omicron BA.2 exceeds 50% of the total number of test results[17], the periods during which omicron BA.1 and BA.2 exceeded 50% of the total number of test results in the genome surveillance data were therefore defined as the "BA.1 dominant period" and the "BA.2 dominant period", respectively.

3 Statistical analysis

We calculated the percentage of patients who reported ADRs for safety evaluation, and the percentage of progressors for clinical outcome evaluation. The cumulative incidence of patients who terminated the observation period was shown by the Kaplan-Meier method in which each reason for observation withdrawal was treated as an event. In the analysis of progressor percentage by SARS-CoV-2 sampling period, 95% confidence intervals (CIs) were calculated using the Clopper-Pearson method for the percentage of progressors in each period in which BA.1 or BA.2 was expected to be dominant in Japan.

For statistical analysis, SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used.

4 Compliance with ministerial ordinances

This study is conducted in accordance with the "Good Post-marketing Study Practice for Drugs or GPSP (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 171, dated 20 December 2004 and MHLW, Pharmaceutical Safety and Environmental Health Bureau [PSEHB] Notification No. 1026-1, dated 26 Octo-

ber 2017)", which is the standard for the appropriate conduct of post-marketing surveillance studies by marketing authorization holders to confirm the safety and effectiveness of drugs after they go on the market in Japan. It is also conducted with the approval of the institutional review board (IRB) (the Ethics Review Committee at Kitamachi Clinic). Patient consent was obtained in accordance with the Declaration of Helsinki, and we did not collect data that can identify individuals.

RESULTS

1 Patient disposition

From 31 January to 19 August 2022, 48 study sites were contracted and 512 patients were enrolled from 32 study sites (The mean±Standard deviation [SD]: 16.0±15.0 patients/site, Min-Max: 1-60 patient(s)/site). Among these patients, CRFs were collected from 346 patients and all of these patients were included in the safety analysis population. Among 346 patients included in the safety analysis population, 246 patients were included in the clinical outcome analysis population, excluding "outpatient" (99 patients) and "other (clinical outcomes)" (1 patient) (**Fig. 1**). Outpatients were excluded from the clinical outcome analysis because no data for clinical outcome evaluation were collected from these patients. The patient who was reported as "other (clinical outcomes)" was temporarily discharged from hospital by the date of observation withdrawal and data for the clinical outcome evaluation during the period in which the patient was out of hospital could therefore not be collected and this patient was excluded from the analysis. No events which met the definition of "progressors" were identified in this patient.

2 Patient characteristics

Characteristics of the 346 patients in the safety analysis population and 246 patients in the clinical outcome analysis population are shown in **Table 1**. Among 346 patients in the safety analysis population, 207 patients (59.8%) were "male" and 139 patients (40.2%), including 1 pregnant woman (≧28 weeks) and 1 breast-feeding woman, were "female". The mean±SD for age was 62.4±19.1 years, and the mean±SD for weight was 64.08±17.62 kg. Regarding hospitalization status at baseline, 247 patients were "inpatient" (71.4%) and 99 were "outpatient" (28.6%). The mean±SD for observation period was 6.1±6.3 days. The most common types of risk factors for progression to severe SARS-CoV-2 infection at baseline were "55 years of age or older" in 228 patients (65.9%), "diabetes mellitus requiring medications" in 58 patients (16.8%), and "obesity (body mass index [BMI] >30 kg/m^2)" in 45 patients (13.0%) (duplicates included). In addition, 22 patients (6.4%) had/received "immunosuppressive disease or immunosuppressive treatment" and 17 patients (4.9%) had "malignant tumour". The severity[6] at baseline was "mild" in 273 patients (78.9%) and "moderate I (no respiratory failure)" in 73 patients (21.1%). The mean±SD number of days from the onset of SARS-CoV-2 symptoms to the date of sotrovimab treatment was 2.7±1.7 days. Among the 21 patients for whom SARS CoV-2 variant information was available, omicron BA.1 was detected in 1 patient and omicron BA.2 was detected in 20 patients. Vaccination against SARS-CoV-2 infection was recorded for 162 patients (46.8%); the number of vaccine doses was "one" in 9 patients (2.6%), "two" in 85 patients (24.6%), and "three" in 68 patients (19.7%). Moreover, 13 patients (3.8%) used SARS-CoV-2 medications other than sotrovimab as a pre-treatment medication, with "antivirals" the most frequently reported (13 patients; 3.8%). Thirty-seven patients (10.7%) used concomitant SARS-CoV-2 medica-

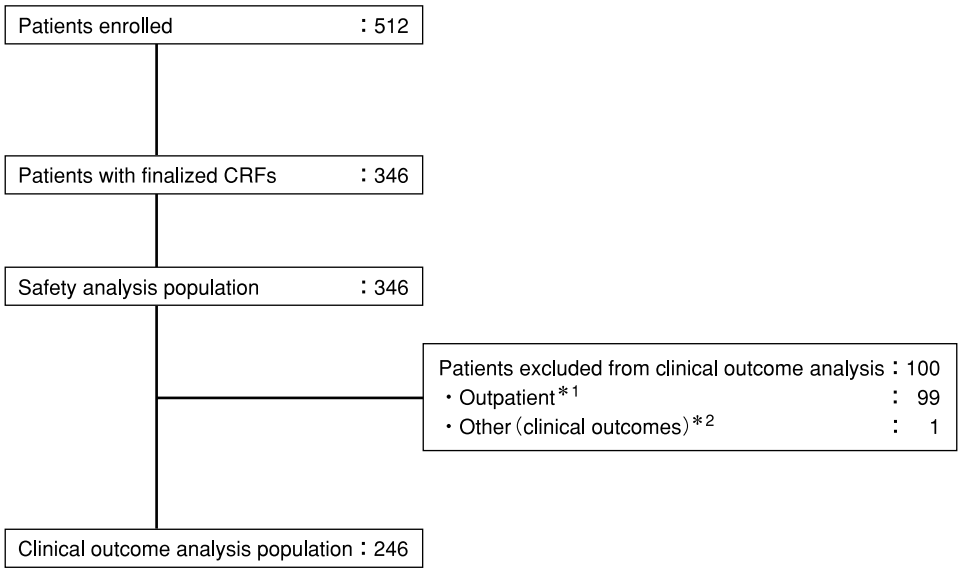


Fig. 1　Patient Disposition

*1: These patients were excluded from clinical outcome analysis, as no data on clinical outcome evaluation were collected from them.

*2: This patient was temporarily discharged from hospital by the date of observation withdrawal. We could not collect data on clinical outcome evaluation during the period in which the patient was out of hospital, therefore, we excluded this patient from clinical outcome analysis. This patient experienced no events which meet the definition of "progressors".

tions other than sotrovimab；"antivirals" and "immunosuppressant medications or modulators" were reported in 36 patients (10.4%) and 9 patients (2.6%), respectively (duplicates included).

The characteristics of the 246 patients included in the clinical outcome analysis population are also shown in **Table 1**, along with patient characteristics by SARS-CoV-2 sampling period (BA.1 and BA.2 dominant periods). The percentage of "male" patients was 68.6% (81/118 patients) and 55.5% (71/128 patients) in the BA.1 and BA.2 dominant periods, respectively. The mean±SD for age was 61.2±21.3 years and 67.3±17.5 years, and the mean±SD for weight was 65.94±18.91 kg and 60.07±13.94 kg, respectively. The proportion of "yes" for comorbidities was 74.6% (88/118 patients) and 81.3% (104/128 patients) in the BA.1 and BA.2 dominant periods, respectively. Vaccination against SARS-CoV-2 infection was reported for 38.1% (45/118 patients) of patients in the BA.1 dominant period and 53.9% (69/128 patients) of patients in the BA.2 dominant period. The percentage of patients with a body temperature of＞37.5℃ at baseline was 33.1% (39/118 patients) in the BA.1 dominant period and 23.4% (30/128 patients) in the BA.2 dominant period. Other patient characteristics were generally similar between patients in the two periods.

3　Observation period (by reason for observation withdrawal)

The observation period by reason for observation withdrawal in 247 patients included in the safety analysis population (inpatients) is demonstrated in **Fig. 2**. Ninety-nine outpatients, whose

Table 1 Patient Characteristics (Composition Ratio) and Safety/Clinical Outcomes by Patient Characteristics (1)
[Safety analysis population, clinical outcome analysis population, As of 19 Aug 2022]

Patient Characteristics		Safety		Clinical outcomes		Clinical outcomes (BA.1 dominant period)		Clinical outcomes (BA.2 dominant period)	
		Safety analysis population (%)	No. of patients with ADRs (%)	Clinical outcome analysis population (%)	No. of progressors (%)	Clinical outcome analysis population (%)	No. of progressors (%)	Clinical outcome analysis population (%)	No. of progressors (%)
Total		346 (100.0)	9 (2.6)	246 (100.0)	1 (0.4)	118 (100.0)	1 (0.8)	128 (100.0)	0 (0.0)
Gender	Male	207 (59.8)	6 (2.9)	152 (61.8)	1 (0.7)	81 (68.6)	1 (1.2)	71 (55.5)	0 (0.0)
	Female	139 (40.2)	3 (2.2)	94 (38.2)	0 (0.0)	37 (31.4)	0 (0.0)	57 (44.5)	0 (0.0)
Age [years][1)]	12 to＜18	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (—)
	18 to＜65	173 (50.0)	7 (4.0)	108 (43.9)	0 (0.0)	59 (50.0)	0 (0.0)	49 (38.3)	0 (0.0)
	≧65	172 (49.7)	2 (1.2)	137 (55.7)	1 (0.7)	58 (49.2)	1 (1.7)	79 (61.7)	0 (0.0)
	Mean±SD	62.4±19.1		64.4±19.7		61.2±21.3		67.3±17.5	
	Min	16		16		16		18	
	Max	98		98		98		97	
	Median (P25-P75)	64.0 (49.0-77.0)		68.0 (50.0-80.0)		64.0 (45.0-78.0)		70.0 (55.5-80.0)	
Oxygenation for SARS-CoV-2 infection at baseline	No	346 (100.0)	9 (2.6)	246 (100.0)	1 (0.4)	118 (100.0)	1 (0.8)	128 (100.0)	0 (0.0)
Types of risk factors for progression to severe SARS-CoV-2 infection at baseline (duplicates included)	55 years of age or older	228 (65.9)	2 (0.9)	172 (69.9)	1 (0.6)	73 (61.9)	1 (1.4)	99 (77.3)	0 (0.0)
	Diabetes mellitus requiring medications	58 (16.8)	0 (0.0)	37 (15.0)	1 (2.7)	14 (11.9)	1 (7.1)	23 (18.0)	0 (0.0)
	Obesity (BMI>30 kg/m^2)	45 (13.0)	1 (2.2)	22 (8.9)	0 (0.0)	15 (12.7)	0 (0.0)	7 (5.5)	0 (0.0)
	Chronic renal disorder (eGFR＜60 mL/min/1.73 m^2)	29 (8.4)	0 (0.0)	24 (9.8)	1 (4.2)	14 (11.9)	1 (7.1)	10 (7.8)	0 (0.0)
	Congestive cardiac failure (≧NYHA Functional Classification Class Ⅱ)	7 (2.0)	0 (0.0)	6 (2.4)	1 (16.7)	4 (3.4)	1 (25.0)	2 (1.6)	0 (0.0)
	Chronic obstructive pulmonary disease (COPD) (chronic bronchitis, COPD or emphysema with dyspnoea on exertion)	24 (6.9)	0 (0.0)	20 (8.1)	0 (0.0)	7 (5.9)	0 (0.0)	13 (10.2)	0 (0.0)
	Moderate to severe asthma (patients who require inhaled corticosteroids for symptom control or who were prescribed oral corticosteroids in the year prior to sotrovimab administration)	33 (9.5)	2 (6.1)	22 (8.9)	0 (0.0)	9 (7.6)	0 (0.0)	13 (10.2)	0 (0.0)
	Other	179 (51.7)	6 (3.4)	106 (43.1)	1 (0.9)	55 (46.6)	1 (1.8)	51 (39.8)	0 (0.0)
	Immunosuppressive disease or immunosuppressive treatment	22 (6.4)	0 (0.0)	9 (3.7)	0 (0.0)	5 (4.2)	0 (0.0)	4 (3.1)	0 (0.0)
	Malignant tumour	17 (4.9)	1 (5.9)	11 (4.5)	0 (0.0)	9 (7.6)	0 (0.0)	2 (1.6)	0 (0.0)

[1)] Age was calculated with imputing date and month with 30th Jun uniformity because only the data about the year of patients' birth were collected in this study from the viewpoint of the protection of personal information.

Table 1 Patient Characteristics (Composition Ratio) and Safety/Clinical Outcomes by Patient Characteristics (2)
[Safety analysis population, clinical outcome analysis population, As of 19 Aug 2022]

Patient Characteristics		Safety		Clinical outcomes		Clinical outcomes (BA.1 dominant period)		Clinical outcomes (BA.2 dominant period)	
		Safety analysis population (%)	No. of patients with ADRs (%)	Clinical outcome analysis population (%)	No. of progressors (%)	Clinical outcome analysis population (%)	No. of progressors (%)	Clinical outcome analysis population (%)	No. of progressors (%)
Total		346 (100.0)	9 (2.6)	246 (100.0)	1 (0.4)	118 (100.0)	1 (0.8)	128 (100.0)	0 (0.0)
Hospitalization status at baseline	Inpatient	247 (71.4)	9 (3.6)	246 (100.0)	1 (0.4)	118 (100.0)	1 (0.8)	128 (100.0)	0 (0.0)
	Outpatient	99 (28.6)	0 (0.0)	0 (0.0)	0 (—)	0 (0.0)	0 (—)	0 (0.0)	0 (—)
Weight [kg]	<40.0	15 (4.3)	0 (0.0)	11 (4.5)	0 (0.0)	6 (5.1)	0 (0.0)	5 (3.9)	0 (0.0)
	40.0 to<100.0	276 (79.8)	8 (2.9)	207 (84.1)	1 (0.5)	91 (77.1)	1 (1.1)	116 (90.6)	0 (0.0)
	≧100.0	14 (4.0)	0 (0.0)	10 (4.1)	0 (0.0)	8 (6.8)	0 (0.0)	2 (1.6)	0 (0.0)
	Unknown	41 (11.8)	1 (2.4)	18 (7.3)	0 (0.0)	13 (11.0)	0 (0.0)	5 (3.9)	0 (0.0)
	Mean±SD	64.08±17.62		62.78±16.64		65.94±18.91		60.07±13.94	
	Min	29.5		29.5		29.5		33.3	
	Max	140.0		125.0		125.0		120.0	
	Median (P25–P75)	62.00 (52.00–74.00)		61.35 (51.25–71.10)		65.00 (52.00–75.00)		59.00 (50.00–67.20)	
BMI [kg/m^2]	<18.5	31 (9.0)	0 (0.0)	23 (9.3)	0 (0.0)	12 (10.2)	0 (0.0)	11 (8.6)	0 (0.0)
	18.5 to<25.0	151 (43.6)	4 (2.6)	120 (48.8)	1 (0.8)	48 (40.7)	1 (2.1)	72 (56.3)	0 (0.0)
	25.0 to<30.0	63 (18.2)	3 (4.8)	45 (18.3)	0 (0.0)	19 (16.1)	0 (0.0)	26 (20.3)	0 (0.0)
	≧30.0	45 (13.0)	1 (2.2)	25 (10.2)	0 (0.0)	17 (14.4)	0 (0.0)	8 (6.3)	0 (0.0)
	Unknown	56 (16.2)	1 (1.8)	33 (13.4)	0 (0.0)	22 (18.6)	0 (0.0)	11 (8.6)	0 (0.0)
	Mean±SD	24.19±5.37		23.65±4.92		24.42±5.71		23.01±4.09	
	Min	13.8		13.8		13.8		14.3	
	Max	44.2		41.3		41.3		38.7	
	Median (P25–P75)	23.35 (20.52–26.47)		22.89 (20.34–25.84)		23.67 (20.67–26.48)		22.66 (20.32–25.40)	
Smoking history	Never-smoker	144 (41.6)	2 (1.4)	91 (37.0)	0 (0.0)	38 (32.2)	0 (0.0)	53 (41.4)	0 (0.0)
	Ever-smoker	86 (24.9)	3 (3.5)	76 (30.9)	1 (1.3)	38 (32.2)	1 (2.6)	38 (29.7)	0 (0.0)
	Currentl smoker	68 (19.7)	4 (5.9)	48 (19.5)	0 (0.0)	28 (23.7)	0 (0.0)	20 (15.6)	0 (0.0)
	Unknown	48 (13.9)	0 (0.0)	31 (12.6)	0 (0.0)	14 (11.9)	0 (0.0)	17 (13.3)	0 (0.0)
Comorbidities	Yes	281 (81.2)	7 (2.5)	192 (78.0)	1 (0.5)	88 (74.6)	1 (1.1)	104 (81.3)	0 (0.0)
Comorbidities (renal impairment)	Yes	30 (8.7)	0 (0.0)	25 (10.2)	1 (4.0)	14 (11.9)	1 (7.1)	11 (8.6)	0 (0.0)
Comorbidities (hepatic impairment)	Yes	8 (2.3)	0 (0.0)	5 (2.0)	0 (0.0)	4 (3.4)	0 (0.0)	1 (0.8)	0 (0.0)
Comorbidities (other)	Yes	277 (80.1)	7 (2.5)	189 (76.8)	1 (0.5)	87 (73.7)	1 (1.1)	102 (79.7)	0 (0.0)
Oxygenation for diseases other than SARS-CoV-2 infection at baseline	No	339 (98.0)	9 (2.7)	240 (97.6)	1 (0.4)	114 (96.6)	1 (0.9)	126 (98.4)	0 (0.0)
	Yes	6 (1.7)	0 (0.0)	6 (2.4)	0 (0.0)	4 (3.4)	0 (0.0)	2 (1.6)	0 (0.0)
	Unknown	1 (0.3)	0 (0.0)	0 (0.0)	0 (—)	0 (0.0)	0 (—)	0 (0.0)	0 (—)

Table 1 Patient Characteristics (Composition Ratio) and Safety/Clinical Outcomes by Patient Characteristics (3)

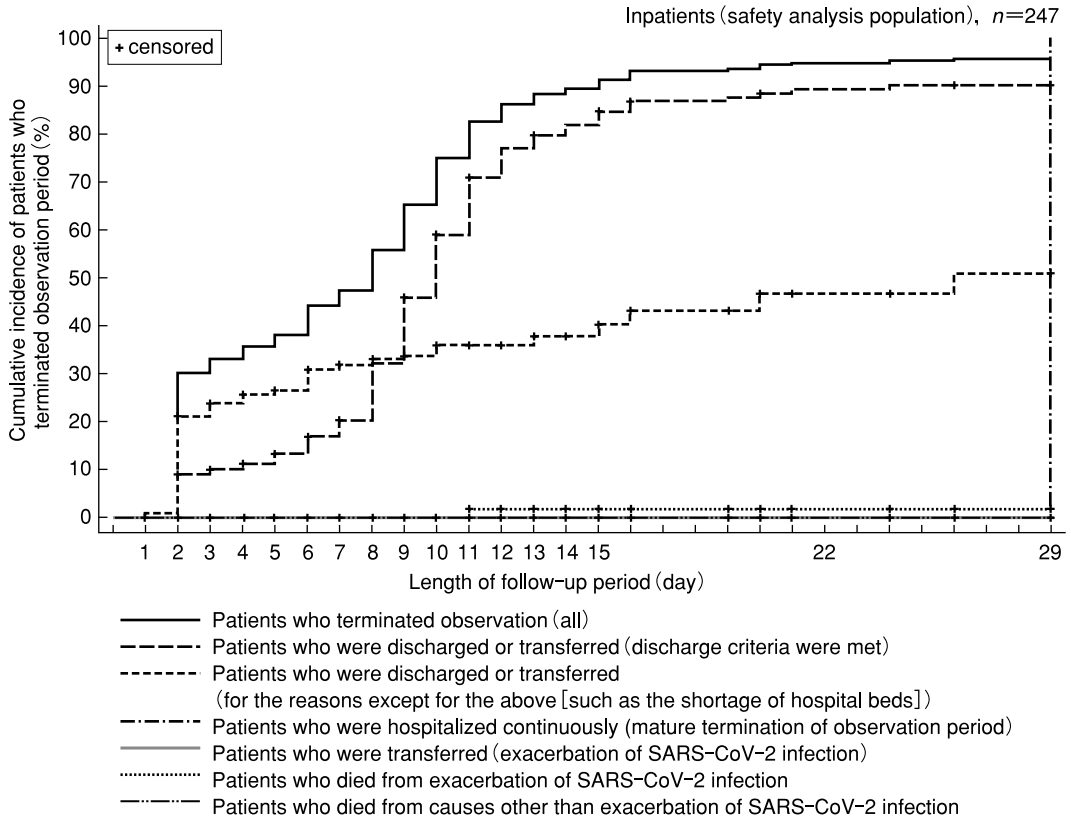
[Safety analysis population, clinical outcome analysis population, As of 19 Aug 2022]

Patient Characteristics		Safety		Clinical outcomes		Clinical outcomes (BA.1 dominant period)		Clinical outcomes (BA.2 dominant period)	
		Safety analysis population (%)	No. of patients with ADRs (%)	Clinical outcome analysis population (%)	No. of progressors (%)	Clinical outcome analysis population (%)	No. of progressors (%)	Clinical outcome analysis population (%)	No. of progressors (%)
Total		346 (100.0)	9 (2.6)	246 (100.0)	1 (0.4)	118 (100.0)	1 (0.8)	128 (100.0)	0 (0.0)
Severity at baseline	Mild	273 (78.9)	8 (2.9)	180 (73.2)	0 (0.0)	86 (72.9)	0 (0.0)	94 (73.4)	0 (0.0)
	Moderate I (no respiratory failure)	73 (21.1)	1 (1.4)	66 (26.8)	1 (1.5)	32 (27.1)	1 (3.1)	34 (26.6)	0 (0.0)
No. of days from the onset of SARS-CoV-2 symptoms to the date of sotrovimab treatment (days)	No SARS-CoV-2 symptoms at baseline	8 (2.3)	0 (0.0)	7 (2.8)	0 (0.0)	1 (0.8)	0 (0.0)	6 (4.7)	0 (0.0)
	≦3	244 (70.5)	5 (2.0)	177 (72.0)	1 (0.6)	86 (72.9)	1 (1.2)	91 (71.1)	0 (0.0)
	4 to 5	73 (21.1)	1 (1.4)	47 (19.1)	0 (0.0)	25 (21.2)	0 (0.0)	22 (17.2)	0 (0.0)
	6 to 7	20 (5.8)	3 (15.0)	14 (5.7)	0 (0.0)	6 (5.1)	0 (0.0)	8 (6.3)	0 (0.0)
	8 to 10	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (—)	1 (0.8)	0 (0.0)
	>10	0 (0.0)	0 (—)	0 (0.0)	0 (—)	0 (0.0)	0 (—)	0 (0.0)	0 (—)
	Mean±SD	2.7±1.7		2.6±1.7		2.6±1.6		2.5±1.8	
	Min	0		0		0		0	
	Max	10		10		7		10	
	Median (P25-P75)	3.0 (2.0-4.0)		2.0 (1.0-4.0)		2.0 (2.0-4.0)		2.0 (1.0-4.0)	
Test for SARS-CoV-2 variants	Not tested	227 (65.6)	9 (4.0)	166 (67.5)	0 (0.0)	80 (67.8)	0 (0.0)	86 (67.2)	0 (0.0)
	Tested	21 (6.1)	0 (0.0)	21 (8.5)	0 (0.0)	0 (0.0)	0 (—)	21 (16.4)	0 (0.0)
	Unknown	98 (28.3)	0 (0.0)	59 (24.0)	1 (1.7)	38 (32.2)	1 (2.6)	21 (16.4)	0 (0.0)
Types of SARS-CoV-2 variants	Omicron	21 (6.1)	0 (0.0)	21 (8.5)	0 (0.0)	0 (0.0)	0 (—)	21 (16.4)	0 (0.0)
	BA.1	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (—)	1 (0.8)	0 (0.0)
	BA.2	20 (5.8)	0 (0.0)	20 (8.1)	0 (0.0)	0 (0.0)	0 (—)	20 (15.6)	0 (0.0)
Vaccination against SARS-CoV-2 infection	No	81 (23.4)	6 (7.4)	73 (29.7)	0 (0.0)	41 (34.7)	0 (0.0)	32 (25.0)	0 (0.0)
	Yes	162 (46.8)	1 (0.6)	114 (46.3)	0 (0.0)	45 (38.1)	0 (0.0)	69 (53.9)	0 (0.0)
	Unknown	103 (29.8)	2 (1.9)	59 (24.0)	1 (1.7)	32 (27.1)	1 (3.1)	27 (21.1)	0 (0.0)
No. of SARS-CoV-2 vaccine doses	One	9 (2.6)	0 (0.0)	8 (3.3)	0 (0.0)	4 (3.4)	0 (0.0)	4 (3.1)	0 (0.0)
	Two	85 (24.6)	0 (0.0)	57 (23.2)	0 (0.0)	32 (27.1)	0 (0.0)	25 (19.5)	0 (0.0)
	Three	68 (19.7)	1 (1.5)	49 (19.9)	0 (0.0)	9 (7.6)	0 (0.0)	40 (31.3)	0 (0.0)
	Four	0 (0.0)	0 (—)	0 (0.0)	0 (—)	0 (0.0)	0 (—)	0 (0.0)	0 (—)
Pre-treatment medications	No	89 (25.7)	1 (1.1)	75 (30.5)	0 (0.0)	41 (34.7)	0 (0.0)	34 (26.6)	0 (0.0)
	Yes	257 (74.3)	8 (3.1)	171 (69.5)	1 (0.6)	77 (65.3)	1 (1.3)	94 (73.4)	0 (0.0)
Pre-treatment medications (SARS-CoV-2 medications)	No	333 (96.2)	9 (2.7)	234 (95.1)	1 (0.4)	112 (94.9)	1 (0.9)	122 (95.3)	0 (0.0)
	Yes	13 (3.8)	0 (0.0)	12 (4.9)	0 (0.0)	6 (5.1)	0 (0.0)	6 (4.7)	0 (0.0)
	Antivirals	13 (3.8)	0 (0.0)	12 (4.9)	0 (0.0)	6 (5.1)	0 (0.0)	6 (4.7)	0 (0.0)
	Neutralizing antibodies	0 (0.0)	0 (—)	0 (0.0)	0 (—)	0 (0.0)	0 (—)	0 (0.0)	0 (—)
	Immunosuppressant medications or modulators	0 (0.0)	0 (—)	0 (0.0)	0 (—)	0 (0.0)	0 (—)	0 (0.0)	0 (—)

Table 1　Patient Characteristics（Composition Ratio）and Safety/Clinical Outcomes by Patient Characteristics（4）

［Safety analysis population, clinical outcome analysis population, As of 19 Aug 2022］

Patient Characteristics		Safety		Clinical outcomes		Clinical outcomes (BA.1 dominant period)		Clinical outcomes (BA.2 dominant period)	
		Safety analysis population（%）	No. of patients with ADRs（%）	Clinical outcome analysis population （%）	No. of progressors （%）	Clinical outcome analysis population （%）	No. of progressors （%）	Clinical outcome analysis population （%）	No. of progressors （%）
Total		346 (100.0)	9 (2.6)	246 (100.0)	1 (0.4)	118 (100.0)	1 (0.8)	128 (100.0)	0 (0.0)
Concomitant medications	No	59 (17.1)	0 (0.0)	47 (19.1)	0 (0.0)	25 (21.2)	0 (0.0)	22 (17.2)	0 (0.0)
	Yes	287 (82.9)	9 (3.1)	199 (80.9)	1 (0.5)	93 (78.8)	1 (1.1)	106 (82.8)	0 (0.0)
Concomitant medications (SARS-CoV-2 medications)	No	309 (89.3)	8 (2.6)	211 (85.8)	0 (0.0)	101 (85.6)	0 (0.0)	110 (85.9)	0 (0.0)
	Yes	37 (10.7)	1 (2.7)	35 (14.2)	1 (2.9)	17 (14.4)	1 (5.9)	18 (14.1)	0 (0.0)
	Antivirals	36 (10.4)	1 (2.8)	34 (13.8)	1 (2.9)	16 (13.6)	1 (6.3)	18 (14.1)	0 (0.0)
	Neutralizing antibodies	0 (0.0)	0 (—)	0 (0.0)	0 (—)	0 (0.0)	0 (—)	0 (0.0)	0 (—)
	Immunosuppressant medications or modulators	9 (2.6)	1 (11.1)	8 (3.3)	0 (0.0)	6 (5.1)	0 (0.0)	2 (1.6)	0 (0.0)
Observation period［days］	1	101 (29.2)	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)
	2 to 7	115 (33.2)	7 (6.1)	115 (46.7)	0 (0.0)	63 (53.4)	0 (0.0)	52 (40.6)	0 (0.0)
	8 to 14	104 (30.1)	2 (1.9)	103 (41.9)	1 (1.0)	38 (32.2)	1 (2.6)	65 (50.8)	0 (0.0)
	15 to 22	13 (3.8)	0 (0.0)	13 (5.3)	0 (0.0)	6 (5.1)	0 (0.0)	7 (5.5)	0 (0.0)
	23 to 29	13 (3.8)	0 (0.0)	13 (5.3)	0 (0.0)	10 (8.5)	0 (0.0)	3 (2.3)	0 (0.0)
	Mean±SD	6.1±6.3		8.1±6.5		8.3±7.6		7.8±5.2	
	Min	1		1		1		1	
	Max	29		29		29		29	
	Median (P25-P75)	2.5 (1.0-9.0)		8.0 (2.0-10.0)		6.0 (2.0-10.0)		8.0 (3.0-10.5)	
Body temperature at baseline［℃］	≦37.5	178 (51.4)	8 (4.5)	177 (72.0)	1 (0.6)	79 (66.9)	1 (1.3)	98 (76.6)	0 (0.0)
	>37.5	69 (19.9)	1 (1.4)	69 (28.0)	0 (0.0)	39 (33.1)	0 (0.0)	30 (23.4)	0 (0.0)
	>37.5 to 38.0	25 (7.2)	1 (4.0)	25 (10.2)	0 (0.0)	14 (11.9)	0 (0.0)	11 (8.6)	0 (0.0)
	>38.0	44 (12.7)	0 (0.0)	44 (17.9)	0 (0.0)	25 (21.2)	0 (0.0)	19 (14.8)	0 (0.0)
	Unknown	99 (28.6)	0 (0.0)	0 (0.0)	0 (—)	0 (0.0)	0 (—)	0 (0.0)	0 (—)
	Mean±SD	37.16±0.93		37.16±0.93		37.28±0.96		37.05±0.90	
	Min	35.1		35.1		35.4		35.1	
	Max	40.6		40.6		40.6		40.1	
	Median (P25-P75)	36.90 (36.50-37.60)		36.90 (36.50-37.60)		37.00 (36.60-37.80)		36.80 (36.50-37.50)	



No. of days of observation up to observation termination (day)		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22	29
No. of risk patients		247	245	173	165	159	153	138	130	109	86	62	43	34	29	26	13	11
No. of patients (cumulative)	Patients who terminated observation (all)	2	74	82	88	94	109	117	138	161	185	204	213	218	221	226	234	247
	Patients who were discharged or transferred (discharge criteria were met)	0	22	24	26	30	36	42	61	83	104	122	131	135	138	142	148	149
	Patients who were discharged or transferred (for the reasons except for the above [such as the shortage of hospital beds])	2	52	58	62	64	73	75	77	78	81	81	81	82	82	83	85	86
	Patients who were hospitalized continuously (mature termination of observation period)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11
	Patients who were transferred (exacerbation of SARS-CoV-2 infection)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Patients who died from exacerbation of SARS-CoV-2 infection	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1
	Patients who died from causes other than exacerbation of SARS-CoV-2 infection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Fig. 2 Observation Period (by Reason for Observation Withdrawal)

observation period was 1 day, were excluded from this analysis because we did not collect the data on reasons for observation withdrawal. The percentage of patients who terminated observation on days 2, 8, 15, 22 and 29 were 30.0% (74/247 patients), 55.9% (138/247 patients), 91.5% (226/247 patients), 94.7% (234/247 patients), and 100.0% (247/247 patients), respectively.

The most common reasons for observation withdrawal were as follows : "discharged or

Table 2　Occurrence of ADRs (Total) [Safety analysis population, As of 19 Aug 2022]

	Total	Serious
No. of patients investigated	346	
No. of patients with ADRs	9	1
Percentage of patients with ADRs (%)	2.6	0.3
Type of ADRs	No. of patients with ADRs (%)	
General disorders and administration site conditions	7 (2.0)	0 (0.0)
Pyrexia	7 (2.0)	0 (0.0)
Infections and infestations	1 (0.3)	1 (0.3)
COVID-19 pneumonia	1 (0.3)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	1 (0.3)
Dyspnoea	1 (0.3)	1 (0.3)
Oropharyngeal pain	1 (0.3)	1 (0.3)
Skin and subcutaneous tissue disorders	1 (0.3)	0 (0.0)
Eczema	1 (0.3)	0 (0.0)

MedDRA/J (25.0)

transferred (discharge criteria were met[6])" (60.3%) and "discharged or transferred (for the reasons except for the above, such as the shortage of hospital beds)" (34.8%).

4　Safety

1) Occurrence of ADRs

In 346 patients included in the safety analysis population, 9 patients (2.6%) experienced ADRs (**Table 2**). The reported ADRs were "pyrexia" (7 patients) and "COVID-19 pneumonia","dyspnoea","oropharyngeal pain" and "eczema" (1 patient each). Of these,"COVID-19 pneumonia","dyspnoea", and "oropharyngeal pain" were reported as serious and occurred in the same patient. All reported ADRs were marked as "recovered" or "recovering".

All reports of "pyrexia" occurred on the day of sotrovimab treatment and were reported as recovered on the same day or the day after sotrovimab treatment. The case of "eczema" occurred on the day following sotrovimab treatment, and the patient was recovering by day 8 after sotrovimab treatment."COVID-19 pneumonia","dyspnoea" and "oropharyngeal pain" were considered by the investigator as suspected to be related to SARS-CoV-2 infection other than sotrovimab.

2) Occurrence of ADRs of special interest (serious hypersensitivity such as anaphylaxis, infusion reactions)

A summary of the concerns in the safety specification from the sotrovimab J-RMP[13] is shown in **Table 3-1**. In 346 patients included in the safety analysis population, ADRs related to "serious hypersensitivity such as anaphylaxis, infusion reactions" were "dyspnoea" and "eczema" in 1 patient each (0.3%) (**Table 3-2**). As mentioned above,"dyspnoea" was reported to be serious and the outcome was "recovering"."Eczema" was non-serious, occurred the day after sotrovimab treatment and was marked as "recovering".

Table 3-1 Summary of concern included in safety specification of J-RMP [As of 19 Aug 2022]

Risk category		Concern in safety specification	Additional pharmacovigilance activity
Safety	Important identified risks	Serious hypersensitivity such as anaphylaxis, infusion reactions	General drug use investigation (this study)
	Important potential risks	N/A	N/A
	Important missing information	N/A	N/A
Effectiveness		N/A	

Table 3-2 Occurrence of ADRs Related to "Serious Hypersensitivity Such as Anaphylaxis, Infusion Reactions"* [Safety analysis population, As of 19 Aug 2022]

	Total	Serious
No. of patients investigated	346	
No. of patients with ADRs	2	1
Percentage of patients with ADRs (%)	0.6	0.3
Type of ADRs	No. of patients with ADRs (%)	
Respiratory, thoracic and mediastinal disorders	1 (0.3)	1 (0.3)
Dyspnoea	1 (0.3)	1 (0.3)
Skin and subcutaneous tissue disorders	1 (0.3)	0 (0.0)
Eczema	1 (0.3)	0 (0.0)

MedDRA/J (25.0)

*The events corresponding to the following 1) or 2) were tabulated as events related to "serious hypersensitivity such as anaphylaxis and infusion reactions".
1) Events which exclude both HLT "Injection Site Reactions"and HLT "Infusion Site Reactions" from "Hypersensitivity (narrow)" in SMQs
2) "Anaphylactic reaction" (broad) in SMQs

5 Clinical outcomes

1) Percentage of progressors

Among 246 patients included in the clinical outcome analysis population, one patient (0.4%, 95%CI : 0.01-2.24) met the definition of progressors (**Table. 4**). This patient received oxygen at a rate of 40 liters/min for SARS-CoV-2 infection on day 11 following sotrovimab treatment and died on the same day. The patient was a male in his 70 s whose severity of SARS-CoV-2 infection at baseline was "moderate I (no respiratory failure)". He had several risk factors for progression to severe SARS-CoV-2 infection at baseline, including "55 years of age or older","diabetes mellitus requiring medications","chronic renal disorder","congestive cardiac failure" and "other" (percutaneous transhepatic gallbladder drainage, obstructive arteriosclerosis of lower extremities). He was administered other antivirals for SARS-CoV-2 infection in addition to

Table 4 Percentage of Progressors by SARS-CoV-2 Sampling Period

［Clinical outcome analysis population, As of 19 Aug 2022］

Sampling date for nucleic acid detection test or antigen test diagnosing as SARS-CoV-2 positive	Clinical outcome analysis population (patients)	Progressors (patients)	Progressors (%)	95% CI* (%)	SARS-CoV-2 variant lineages in Japan (%)							SARS-CoV-2 variant lineages in Japan (%)							The most common SARS-CoV-2 variant lineage in Japan
					Genome surveillance data from NIID[1]							Genome surveillance data based on samples from private testing institutions[2]							
					Period investigated	Delta (%)	Omicron				Other (%)	Sampling week (in 2022)	Omicron BA.2			Omicron BA.5			
							BA.1 (%)	BA.2 (%)	BA.4 (%)	BA.5 (%)			Total no. of tests	No. of detections	(%)	Total no. of tests	No. of detections	(%)	
Clinical outcome analysis population	246	1	0.4	0.01-2.24	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
31 Jan 2022-27 Mar 2022	118	1	0.8	0.02-4.63	—	—	—	—	—	—	—	—	—	—	—	—	—	—	Omicron BA.1
31 Jan 2022-6 Feb 2022	13	0	0.0	—	31 Jan 2022-6 Feb 2022	1.0	96.6	0.6	—	—	1.8	5th week	401	6	1.5	—	—	—	
7 Feb 2022-13 Feb 2022	17	0	0.0	—	7 Feb 2022-13 Feb 2022	0.4	94.8	1.5	—	—	3.3	6th week	403	12	3.0	—	—	—	
14 Feb 2022-20 Feb 2022	16	1	6.3	—	14 Feb 2022-20 Feb 2022	0.2	94.9	3.2	—	—	1.7	7th week	399	16	4.0	—	—	—	
21 Feb 2022-27 Feb 2022	18	0	0.0	—	21 Feb 2022-27 Feb 2022	0.2	90.8	6.3	—	—	2.7	8th week	400	39	9.8	—	—	—	
28 Feb 2022-6 Mar 2022	14	0	0.0	—	28 Feb 2022-6 Mar 2022	0.1	87.5	9.9	—	—	2.5	9th week	400	68	17.0	—	—	—	
7 Mar 2022-13 Mar 2022	14	0	0.0	—	7 Mar 2022-13 Mar 2022	0.0	77.9	19.1	—	—	3.0	10th week	400	76	19.0	—	—	—	
14 Mar 2022-20 Mar 2022	13	0	0.0	—	14 Mar 2022-20 Mar 2022	0.0	69.2	27.9	—	—	2.8	11th week	400	128	32.0	—	—	—	
21 Mar 2022-27 Mar 2022	13	0	0.0	—	21 Mar 2022-27 Mar 2022	0.0	58.4	40.0	—	—	1.6	12th week	400	193	48.3	—	—	—	
28 Mar 2022-19 Jun 2022	128	0	0.0	0.00-2.84	—	—	—	—	—	—	—	—	—	—	—	—	—	—	Omicron BA.2
28 Mar 2022-3 Apr 2022	16	0	0.0	—	28 Mar 2022-3 Apr 2022	—	—	—	—	—	—	13th week	563	365	64.8	—	—	—	
4 Apr 2022-10 Apr 2022	25	0	0.0	—	4 Apr 2022-10 Apr 2022	0.0	30.6	68.3	—	—	1.1	14th week	806	587	72.8	—	—	—	
11 Apr 2022-17 Apr 2022	24	0	0.0	—	11 Apr 2022-17 Apr 2022	0.0	20.1	78.9	—	—	1.0	15th week	792	655	82.7	—	—	—	
18 Apr 2022-24 Apr 2022[3]	10	0	0.0	—	18 Apr 2022-24 Apr 2022	0.0	14.0	85.2	—	—	0.8	16th week	778	688	88.4	—	—	—	
25 Apr 2022-1 May 2022	15	0	0.0	—	25 Apr 2022-1 May 2022	0.0	8.1	90.5	—	—	1.4	17th week	843	796	94.4	843	0	0.0	
2 May 2022-8 May 2022	5	0	0.0	—	2 May 2022-8 May 2022	0.0	4.5	94.2	—	—	1.3	18th week	764	749	98.0	764	0	0.0	
9 May 2022-15 May 2022	10	0	0.0	—	9 May 2022-15 May 2022	—	—	—	—	—	—	19th week	1053	1039	98.7	1053	0	0.0	
16 May 2022-22 May 2022	8	0	0.0	—	16 May 2022-22 May 2022	0.0	2.2	96.8	—	—	1.0	20th week	800	787	98.4	800	0	0.0	
23 May 2022-29 May 2022	6	0	0.0	—	23 May 2022-29 May 2022	0.0	1.3	97.6	—	0.1	1.0	21st week	800	797	99.6	800	0	0.0	
30 May 2022-5 Jun 2022	6	0	0.0	—	30 May 2022-5 Jun 2022	—	—	—	—	—	—	22nd week	788	779	98.9	791	4	0.5	
6 Jun 2022-12 Jun 2022	2	0	0.0	—	6 Jun 2022-12 Jun 2022	0.0	0.4	97.3	—	1.4	0.9	23rd week	388	385	99.2	807	13	1.6	
13 Jun 2022-19 Jun 2022	1	0	0.0	—	13 Jun 2022-19 Jun 2022	0.0	0.2	91.8	0.5	6.3	1.2	24th week	—	—	—	783	41	5.2	

[1] Novel Coronavirus Infection Measures Advisory Board Material 4 (MHLW)

[2] Novel Coronavirus Infection Measures Advisory Board Material 3-2 (MHLW)

[3] The following warning statement was added to the Patient Insert of sotrovimab on 18 April 2022 ;

"For omicron (B.1.1.529/BA.2), sotrovimab should be considered for administration when other medications cannot be administered, because the effectiveness of sotrovimab may be decreased."

*Clopper-Pearson 95% CI

sotrovimab.

2) Percentage of progressors by SARS-CoV-2 sampling period

Table 4 shows the percentage of progressors by SARS-CoV-2 sampling period. In the BA.1 dominant period (31 January to 27 March 2022), 0.8% (1/118 patients, 95% CI：0.02-4.63) progressed to severe SARS-CoV-2 infection. In the BA.2 dominant period (28 March to 19 June 2022), the progressor percentage was 0.0% (0/128 patients, 95% CI：0.00-2.84).

3) Percentage of progressors by type of SARS-CoV-2 variant

Of the 246 patients included in the clinical outcome analysis population, 8.5% (21/246 patients) were "tested" for SARS-CoV-2 variants. Among these 21 patients tested, one patient reported omicron BA.1 and 20 patients reported omicron BA.2. No progressors were reported in 21 patients who were identified as having omicron BA.1 or BA.2 (**Table 1**).

Of the 20 patients who were identified as having omicron BA.2, 18 patients were "55 years of age or older". The severity[6] of SARS-CoV-2 infection at baseline was "mild" in 17 patients and "moderate I (no respiratory failure)" in 3 patients. With respect to the question："Are you vaccinated against SARS-CoV-2?", 7 patients answered "no", 12 patients answered "yes", and one patient answered "unknown". Among the 12 vaccinated patients, the number of vaccine doses was "three" in 10 patients and "two" in 2 patients. No patients used concomitant medications for SARS-CoV-2 infection. The mean±SD observation period was 8.5±6.0 days. Regarding patient outcomes at the end of the observation period, one patient was "hospitalized", and 19 patients were "discharged or transferred". The reasons for discharge or transfer in these 19 patients were as follows："discharge criteria[6] were met" in 11 patients and "except for the above, such as the shortage of hospital beds" in 8 patients.

4) Patient outcomes at the end of the observation period in patients other than progressors

Among the 246 patients included in the clinical outcome analysis population, 99.6% (245/246 patients) did not meet the criteria for progressors during the observation period. Regarding patient outcomes at the end of the observation period in patients other than progressors, 4.5% (11/246 patients) were "hospitalized" (hospitalized continuously from the date of sotrovimab treatment to day 29) without meeting the definition of progression. 60.2% (148/246 patients) were "discharged or transferred as discharge criteria[6] were met", and 35.0% (86/246 patients) were "discharged or transferred for the reasons except for the above (such as the shortage of hospital beds)". The mean±SD for length of hospitalization was 29.0±0.0 days, 8.8±4.2 days, and 4.2±4.2 days, respectively.

DISCUSSION

This general drug use investigation (observational study) is being conducted to evaluate the safety and clinical outcomes of sotrovimab in real-world clinical practice. This interim report did not identify any new concerns regarding the safety and clinical outcomes of sotrovimab when used in patients infected with SARS-CoV-2 who have risk factors for progression to severe disease and do not require oxygen therapy.

As mentioned above, in Japan, each prefecture determines whether or not a patient infected with SARS-CoV-2 should be hospitalized based on the severity of symptoms, the presence or absence of risk factors for progression to severe SARS-CoV-2 infection, and the number of patients infected with SARS-CoV-2 in each region[14]. Of 346 patients in the safety analysis population of this study, 71.4% (247/346 patients) were hospitalized at baseline. In Japan,

sotrovimab is indicated for use in "patients who have risk factors for progression to severe infection caused by SARS-CoV-2 and do not require oxygen therapy"[11]. In the safety analysis population, 78.9% were categorized as "mild" and 21.1% as "moderate I (no respiratory failure)" in severity at baseline. Given these facts, although their SARS-CoV-2 infection was not considered to be severe, these hospitalized patients (247 patients) may have been considered for hospitalization as a precautionary measure in consideration of risk factors for progression to severe SARS-CoV-2 infection.

The percentage of patients in the safety analysis population who reported ADRs was 2.6% (9/346 patients). This proportion is slightly higher than the 1.5% (8/523 patients) reported in the sotrovimab arm of the overseas phase Ⅱ/Ⅲ clinical trial (COMET-ICE)[9] and the 0.0% (0/18 patients) reported for Japanese and Caucasian healthy adults in the overseas phase Ⅰ clinical trial[12], although direct comparisons may not be appropriate due to differences in patient characteristics and study methods. Pyrexia and eczema reported in this study were non-serious, and patients who reported these ADRs were recovered or recovering. Regarding COVID-19 pneumonia, dyspnoea and oropharyngeal pain, the investigator reported SARS-CoV-2 infection as the factor related to occurrence of these AEs other than sotrovimab. Therefore, these ADRs were not considered to represent new safety concerns with sotrovimab.

"Serious hypersensitivity such as anaphylaxis, infusion reactions" is included as a concern in the safety specification of the J-RMP for sotrovimab[13] and was therefore identified as an ADR of special interest in this study. The ADRs related to "serious hypersensitivity such as anaphylaxis, infusion reactions" reported in this study were "dyspnoea" and "eczema" in 1 patient each. "COVID-19 pneumonia" was reported as an ADR in the same patient who reported "dyspnoea". Since the investigator reported SARS-CoV-2 infection as the factor related to occurrence of "dyspnoea" other than sotrovimab (as described above), it was thought unlikely that it would correspond to "serious hypersensitivity such as anaphylaxis, infusion reactions". The patient who reported "eczema" did not report any other symptoms (e.g. respiratory, mucosal, gastrointestinal, and cardiovascular). According to the Brighton Collaboration case definition of anaphylaxis[18], "eczema" in this patient was not considered to meet the definition of anaphylaxis. Based on these interim findings, it was thought unnecessary to consider new safety measures related to "serious hypersensitivity such as anaphylaxis, infusion reactions". In the overseas phase Ⅱ/Ⅲ clinical trial (COMET-ICE), 2% (9/523 patients) of patients in the sotrovimab arm reported events corresponding to "hypersensitivity (narrow)" in the SMQ, and 1% (6/523 patients) experienced reactions associated with systemic infusion observed within 24 hours of the start of sotrovimab treatment[8,9,13]. In another overseas phase Ⅲ study (Accelerating COVID-19 Therapeutic Interventions and Vaccines [ACTIV-3]), one patient reported serious anaphylaxis for which a causal relationship with sotrovimab could not be ruled out[13,19]. Therefore, the occurrence of ADRs related to "serious hypersensitivity such as anaphylaxis, infusion reactions" should continue to be monitored. Also, the following limitations should be considered in relation to the safety data from this analysis: 1) it is possible that these data were affected by selection bias because of a central enrollment method by which investigators enrolled patients within 14 days after the date of sotrovimab administration; 2) we have been unable to collect ADRs that occurred after day 2 in outpatients and after

the date of discharge from hospital or transfer to another hospital in inpatients who left of hospital before day 29；3) it is possible that ADRs were under-reported in this study, given that such reports were made by investigators based on their judgement.

The percentage of progressors in the clinical outcome analysis population of this study was 0.4% (1/246 patients). In the above-mentioned overseas phase Ⅱ/Ⅲ clinical trial (COMET-ICE),"hospitalization or death within 29 days after sotrovimab treatment (for any cause)" was evaluated as the primary efficacy outcome and occurred in 1.1% (6/528 patients) of patients in the sotrovimab arm[9]. We cannot compare directly between these studies because the criteria for hospitalization of patients infected with SARS-CoV-2 are different between North/South America and Europe (where the COMET-ICE was conducted) and Japan, and the methods for evaluating efficacy and clinical outcomes differ in these studies. Nevertheless, the percentage of progressors in this study (0.4%, 1/246 patients) was slightly lower than the proportion of patients who progressed to severe or critical respiratory COVID-19 through day 29 (1%, 7/528 patients), which was evaluated as secondary endpoint in the COMET-ICE trial[9]. This interim analysis did not identify any concerns about the clinical outcomes with sotrovimab at present.

Among the 246 patients in the clinical outcome analysis population in this study, 21 had data available for SARS-CoV-2 variants. Of these, 20 patients were known to be infected with omicron BA.2, and none of these patients progressed. Similarly, the progressor percentage in the BA.2 dominant period was 0.0% (0/128 patients). *In vitro* neutralization assay using the clinical isolate BA.2 showed a 15.7 and 35.1-fold increase in EC_{50} and EC_{90}, respectively, compared with the wild-type, based on experiments in VeroE6 cells expressing the transmembrane serine protease 2 (TMPRSS2). Therefore, the Package Insert for sotrovimab in Japan was updated on 18 April 2022[11] to include the following: "For omicron (B.1.1.529/BA.2), sotrovimab should be considered for administration when other medications cannot be administered, because the effectiveness of sotrovimab may be decreased." However, the interim results of this study provided no data suggesting that the effectiveness of sotrovimab against omicron BA.2 is decreased at this point. Recent reports from France, the United States and the United Kingdom demonstrated sotrovimab's protective role in preventing COVID-19 progression in BA.2 infected patients as well as BA.1 infected patients[20-22], consistent with the results from our study.

Sotrovimab has Fc effector functions, including antibody-dependent and cell cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), and has also been demonstrated *in vitro* to directly neutralize SARS-CoV-2[7]. Although the clinical significance of antibody Fc effector functions during COVD-19 is not known, Case et al. (2022)[23] reported significant Fc effector functions in an *in vivo* preclinical animal model (Syrian hamster) using S309 (the parent mAb of sotrovimab). Thus, Fc effector functions may contribute to the anti-viral activity of sotrovimab. These Fc effector functions in antibodies are important for defense against virus infection, whereas it has been reported that these functions are related to antibody-dependent enhancement (ADE) and might exacerbate virus infection[24]. However, it was reported that the infectivity-enhancing antibody in patients infected by SARS-CoV-2 recognized a specific site on the N-terminal domain (NTD) of the SARS-CoV-2 spike protein[25], and sotrovimab recognizes a different domain from the infectiv-

ity-enhancing antibody. Although ADE was not evaluated in this study, it was assumed that there were few concerns about ADE with sotrovimab, because no ADE-related AEs were reported in the above-mentioned overseas phase Ⅱ/Ⅲ clinical trial (COMET-ICE)[9]. In addition, a recent report[26] indicates that sotrovimab does not have ADE potential *in vitro*.

The following limitations should be noted when considering clinical outcome data from this study: 1) it is an observational study with a single-arm design rather than a randomized, controlled study; 2) it is possible that these data were affected by selection bias because of a central enrollment method by which investigators enrolled patients within 14 days after the date of sotrovimab administration; 3) 246 patients in the clinical outcome analysis population of this study included 35.0% who were discharged from hospital or transferred to another hospital due to the shortage of hospital beds, etc. without meeting the discharge criteria[6] for SARS-CoV-2 infection in Japan (patients who were not observed sufficiently until they recovered from SARS-CoV-2 infection); 4) there are no restrictions on the concomitant use of SARS-CoV-2 medications other than sotrovimab in this study; 5) we have been unable to evaluate clinical outcomes (effectiveness) in outpatients.

Omicron BA.5 is the dominant variant in Japan as of August 2022[27]. Sotrovimab was shown to have a moderate decrease in potency (EC_{50}) against vesicular stomatitis virus (VSV) pseudoviruses expressing BA.5 protein (22.6-fold) and authentic isolates of BA.5 (21.6-fold) compared with wild-type (Wu-G614)[28]. Although sotrovimab retains Fc effector functions against BA.5[29], the effectiveness of sotrovimab against BA.5 in a real-world setting is currently unknown. Omicron BA.2.75 has also been reported as a variant of concern (VOC); sotrovimab had a moderate (8.3-fold) decrease in potency against VSV pseudoviruses expressing BA.2.75 protein, compared with wild-type (Wu-G614)[28]. It is considered that the neutralizing activity against omicron BA.2.75 is slightly higher than that against BA.5, but again the effectiveness of sotrovimab against BA.2.75 in a real-world setting is unknown. Data on the real-world safety and effectiveness of sotrovimab against VOC including omicron BA.5 are expected in the near future from this ongoing study in Japan.

CONCLUSIONS

In the interim analysis of this study, no new issues were identified concerning the safety and clinical outcomes of sotrovimab in patients infected with SARS-CoV-2 in real-world clinical practice. The study is ongoing and will provide additional data on the real-world safety and effectiveness of sotrovimab.

CONFLICT OF INTEREST

All authors are employees of GSK, and 7 of these authors (Yasuyo Nose, Hiroko Mizohata, Akemi Kaneuchi, Kenji Oda, Yutaka Handa, Takako Hattori, Naohiro Takahashi) hold shares in GSK.

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